Remarks

The January 5, 2004 Official Action has been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the January 5, 2004 Official Action. Therefore, the initial due date for response is April 5, 2004.

At the outset, the Examiner has objected to the amendment of the specification at page 5, lines 12-20 for allegedly introducing new matter into the specification. Applicants have amended the phrase allegedly containing new matter to read as originally filed. Applicants submit that the intent of the original amendment was to simply make the sentence clearer and not to add new matter, as perceived by the Examiner.

The Examiner has rejected claims 3, 4, and 6-9 for allegedly failing to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

At pages 6-18 of the Official Action, the Examiner has also rejected claims 3, 4, and 6-9 for allegedly failing to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

The Examiner has also rejected claims 3, 4, and 6-9 under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, it is the Examiner's position that the metes and bounds of the term "signature" are unclear as the term is allegedly not defined by the specification.

The foregoing rejections constitute all of the grounds set forth in the January 5, 2004 Official Action for refusing the present application.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

CLAIMS 3, 4, AND 6-9, AS AMENDED, SATISFY THE ENABLEMENT REQUIREMENTS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 3, 4, and 6-9 for allegedly failing to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph for several reasons.

First, it is the Examiner's position that the specification does not provide guidance as to how to distinguish between Barrett's esophageal condition and any other cancerous or precancerous condition of the esophagus. In an effort to expedite prosecution of the instant application, Applicants have amended claims 3 and 7 to recite the further step of confirming the diagnosis of Barrett's esophageal condition by performing a biopsy. Support for this amendment can be found at, for example, page 14, line 17 through page 15, line 14 and at page 3, lines 9-27.

Applicants have also added claims 13-17 wherein a method for screening for the presence of Barrett's esophagus condition is provided. Support for new claims 13-18 can be found in current claims 3, 4, and 6-9. Additionally, support can be found throughout the specification at, for example, page 3, lines 9-27, wherein it is disclosed that "the leakage of signature carbohydrates serves as the basis for a noninvasive ... screen for upper GI cancers for precancerous and cancerous conditions" and that the tests "can alert the physician to the need for the more expensive and involved endoscopic ... procedures."

Second, the Examiner alleges that the specification, while enabling for assaying sucrose levels in urine, is not enabling for the genus of signature carbohydrates as claimed. In the instant application, Applicants have identified mannitol and sucrose as signature carbohydrates for use in the instantly claimed invention. As noted by the Examiner at page 4 of the instant Official Action, the specification is enabling for assaying urine for elevated levels of sucrose to diagnose Barrett's esophageal condition. Furthermore, the

Examiner acknowledges that Applicants have demonstrated the ability of mannitol to be employed for assaying the permeability of tight junctions *in vitro*. However, it is the Examiner's position that the specification fails to teach that mannitol could diffuse into the bloodstream and "arrive in the urine in an undegraded state."

Applicants respectfully disagree. It is a well settled premise in patent law that a patent need not teach, and preferably omits, what is well known in the art. Lindemann Maschinenfabrik v. American Hoist and Derrick, 221 USPQ 481, 489 (Fed. Cir. 1984). Furthermore, as noted in the MPEP at § 2164.01,

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the *disclosures in the patent coupled with information known in the art* without undue experimentation. (Emphasis added).

Applicants respectfully submit that, prior to the instant invention, it was known that mannitol could be administered to a patient by ingestion and detected in the urine in order to identify intestinal permeability (see pages 3547 and 3548 of Smecuol et al. (Am. J. Gastroen. (1999) 94:3547-3552). Thus, Applicants submit that a skilled artisan, apprised of the ability to monitor ingested mannitol in a patient's urine, would clearly be able to use the instantly claimed invention in light of the disclosures that 1) Barrett's esophagus condition can be diagnosed by monitoring sucrose in levels in urine and 2) mannitol can be used to assay tight junction permeability in *in vitro* assays.

Lastly, the Examiner contends that the specification fails to provide adequate guidance or working examples for the *in vivo* use of monitoring protein expression or the phosphorylation state of occludin to determine tight junction leakiness, as set forth in claims 8 and 9, respectively. It is the Examiner's position that cells in culture "exhibit characteristics different from those *in vivo* and cannot

duplicate the complex conditions of the *in vivo* environment." Thus, according to the Examiner, "no one of skill in the art would believe it more likely than not that the claimed alterations in phosphorylation state and expression levels would be altered in the same way in the *in vivo* condition."

Applicants strenuously disagree with the Examiner's position. While Applicants agree with the Examiner that *in vitro* assays do not fully duplicate the complex conditions of the *in vivo* environment, Applicants submit that the invention as claimed in claims 8 and 9 relates to cells that have been removed from the complex *in vivo* environment. Applicants also submit that a skilled artisan would recognize that *in vitro* results commonly have correlations and relevance to *in vivo* results. The assertion made by the Examiner that **no** skilled artisan would "believe it more likely than not" that *in vitro* effects would be seen *in vivo* is wholly inaccurate. If such an assertion were true, then all cell culture work would cease to be performed as any results obtained from cell culture work would be deemed wholly irrelevant. Clearly this is not the case.

Applicants also respectfully submit that the test for enablement is the balancing of several specifically prescribed factors listed in MPEP § 2164.01(a), as follows:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.

(Citation omitted.)

It is the Applicants position that the factors set forth in MPEP § 2164.01(a) support the conclusion that the instantly claimed invention is fully enabled. Specifically, the claims are not particularly broad, artisans in the relevant field are highly skilled, and the field is predictable. *In vitro* assays for detecting the presence and phosphorylation state of a protein have been established and Applicants have provided explicit directions for performing the claimed invention (see, for example, page 15, lines 15-26). Thus, the amount of experimentation needed to "make and use" the claimed invention is minimal.

Applicants also submit that, at the time of the instant invention, a correlation between *in vitro* data and *in vivo* results had been established in reference to occludin phosphorylation and tight junction integrity. Indeed, close examination of Clarke et al., cited in the instant application at page 11, line 8 in reference to the phosphorylation of occludin, reveals that the phosphorylation of occludin had been studied *in vivo* (see page 3188). More specifically, Sakakibara et al. (J. Cell Biol. (1997) 137:1393-1401) teach that phosphorylated occludin is "selectively concentrated at the tight junction" in biopsies of chick intestinal epithelial cells (see page 1397 and Fig. 8). Inasmuch as the *in vivo* data is consistent with the *in vitro* data that phosphorylation of occludin directly corresponds with the integrity of tight junctions, Applicants submit that a skilled artisan would be able to perform the instantly claimed invention without undue experimentation.

As to the monitoring of protein expression to determine tight junction leakiness, Applicants have amended the claim to recite ZO-1 instead of the genus of protein for the reasons set forth hereinbelow. Applicants again submit that a skilled artisan at the time of the invention would have

been apprised of the *in vivo* studies regarding ZO-1 and tight junctions. Indeed, Gottardi et al. (Proc. Natl. Acad. Sci. (1996) 93:10779-10784) show that ZO-1 is predominantly localized to the tight junctions of intestinal epithelial cells present in a tissue section obtained from a dog (see Fig. 5). Additionally, Gottardi et al. show a weaker nuclear staining of ZO-1 in cells that are exfoliating and no longer extensively involved in the formation of tight junctions (see Fig. 5 and pages 10782). Thus, Applicants submit the *in vivo* data of Gattardi et al. demonstrating the increased presence of ZO-1 in cells forming tight junction coincides with the *in vitro* data of the instant application indicating that increased permeability of tight junction correlates with ZO-1 down regulation (page 11, lines 5-8). Because of the correlation between the *in vivo* and *in vitro* data, Applicants submit that a skilled artisan would have a reasonable expectation of success in performing the instant invention. Accordingly, the instantly claimed invention is fully enabled based on the disclosures of the specification and information known in the art.

In light of all of the foregoing, Applicants respectfully request the withdrawal of the enablement rejections of claims 3, 4, and 6-9 under 35 U.S.C. §112, first paragraph.

CLAIMS 3, 4, AND 6-9, AS AMENDED, SATISFY THE WRITTEN DESCRIPTION REQUIREMENTS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 3, 4, and 6-9 have also been rejected for allegedly failing to satisfy the written description requirement under 35 U.S.C. §112, first paragraph for several reasons.

First, the Examiner contends that the term "signature carbohydrate" is inadequately described by the specification. It is the Examiner's position that the

specification "fails to describe the signature carbohydrates to be used in the claimed assay by the test set out in Lilly." Applicants submit that the identification of sucrose and mannitol as "signature carbohydrates" (see page 4, lines 14-15) is sufficient to describe a "representative number" of species. However, Applicants have amended the claims to no longer recite "signature carbohydrates" thereby obviating this rejection.

Second, the Examiner contends the genus of "protein," as stated in claim 8, is not adequately described because only the downregulation of ZO-1 is provided and no common feature of the genus is provided. Applicants have amended claim 8 to specifically recite ZO-1 instead of the genus of "protein." Support for this amendment can be found at page 11, lines 5-6.

Lastly, it is the Examiner's position that the specification fails to provide support for the claim limitation of diagnosing Barrett's esophageal condition by assaying a urine sample for a signature carbohydrate. Specifically, the Examiner contends the only reference in the specification drawn to diagnosing Barrett's esophageal condition refers to assaying serum levels for salivary amylase. Applicants strenuously disagree with the Examiner's contention. Indeed, at page 5, lines 32-33, Barrett's esophagus is defined as a precancerous condition. Additionally, the specification discloses that it is another object of the present invention to "provide a method of diagnosing precancerous ... conditions in a mammal by detecting the backleak of at least one signature carbohydrate" (page 4, lines 11-15) and that the present invention "relates to detecting "precancerous conditions by leakage of signature carbohydrates from the epithelium into the bloodstream" (page 2, lines 21-23). Lastly, at page 6, lines 1-3, the leakage of sucrose, a signature carbohydrate, across the "gastroesophageal mucosa into the bloodstream is analyzed in

an overnight urine sample." Inasmuch as Barrett's esophagus is taught to be a precancerous condition and the specification teaches diagnosing precancerous conditions by detecting signature carbohydrates in urine samples, the specification clearly teaches diagnosing Barrett's esophagus condition by detecting signature carbohydrates in a urine sample. Nothing more is needed to meet the written description requirement under 35 U.S.C. §112, first paragraph.

In view of the foregoing remarks and amendments, Applicants respectfully request the withdrawal of the written description rejections of claims 3, 4, and 6-9 under 35 U.S.C. §112, first paragraph.

CLAIMS 3, 4, AND 6-9, AS AMENDED, SATISFY THE REQUIREMENTS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has additionally rejected claims 3, 4, and 6-9 under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, it is the Examiner's position that the metes and bounds of the term "signature" are unclear as they are allegedly not defined by the specification.

Applicants continue to disagree with the Examiner for the reasons set forth hereinabove. Inasmuch as the allegedly indefinite term "signature" has been deleted from all pending claims, Applicants respectfully request the withdrawal of the rejection of claims 3, 4, and 6-9 under 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the rejections set forth in the January 5, 2004 Official Action be withdrawn and that this application be passed to issue. Indeed, the claimed subject matter, as amended, now reads on methods for detection of sucrose and mannitol in urine as an

indicator of the presence of a precancerous condition, which is enabled by the disclosure in the specification and information known previously in the art. Further, claim 3 has been amended to require an endoscopic biopsy to confirm the diagnosis of Barrett's esophageal precancerous condition. As mentioned, this recitation finds support at pages 14 and 15 of the specification. Lastly, new claims 13-17 have been added to emphasize the use of the current invention as a preliminary screen for identifying the presence of Barrett's esophageal precancerous condition.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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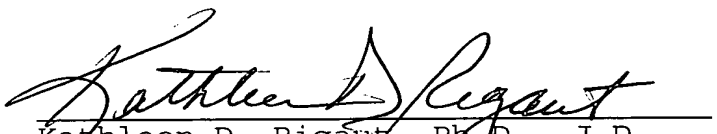
By 
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Enclosures: Sakakibara et al.
(J. Cell Biol. (1997) 137:1393-1401)
Smecuol et al.
(Am. J. Gastroen. (1999) 94:3547-3552)
Gottardi et al.
(Proc. Natl. Acad. Sci. (1996) 93:10779-10784)